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# A Short and Efficient Synthesis of (-)-Ambrox® from (-)-Sclareol using a Ruthenium Oxide Catalyzed Key Step.

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***Abstract** : (-)-Ambrox®5 has been synthesized in 3 steps from natural (-)-sclareol 1. Depending on the reoxidizing agents and the reaction conditions used in the ruthenium oxide catalyzed key step, overall yields of 79% ($NaIO_4/RuO_4$) or 48% ($Ca(OCl)_2/RuO_4$-) were observed.*

Due to its unique olfactive and fixative properties the (-)-norlabdane oxide **5**, more commonly known under the trade name Ambrox®(Firmenich), constitutes today the commercially most important substitute for ambergris[1], a metabolite to the blue sperm whale[2], which thanks to increasing whale protection is practically not any more used in perfumery. This compound was synthesized for the first time by Stoll and Hinder in 1950[3] and it was only much later that it was found to occur naturally in trace amounts in ambergris itself[4], the essential oils of cyprus *Cupressus sempervivens L*[5], clary sage *Salvia sclarea L*[6] and cistus *Cistus labdaniferus L*[6] as well as in the absolute of tobacco *Nicotiana tabacum*[7]. Meanwhile an impressive synthetic activity[8] has developed around this molecule heading either for its racemic or optically active form. Regarding the preparation of (-)-Ambrox®5, whose odor is somewhat different from the racemic material, different strategies have been pursued which include an enzymatically catalyzed biomimetic approach[9] and a total synthesis with an optical resolution step incorporated[10].

Most of these successful syntheses however have started from naturally occurring sequi- or diterpenes such as (-)-drimenol[11], (-)-labdanolic acid[12], (-)-abietic acid[13] and above all (-)-sclareol 1[14], thereby taking advantage of the correct stereochemical set up of 3 continuous chiral centers present in these molecules. Approaches starting from(-)-sclareol **1**, which itself can be obtained from the concrete of clary sage *Salvia sclarea L;*[15] or of novel lines of the tobacco plant

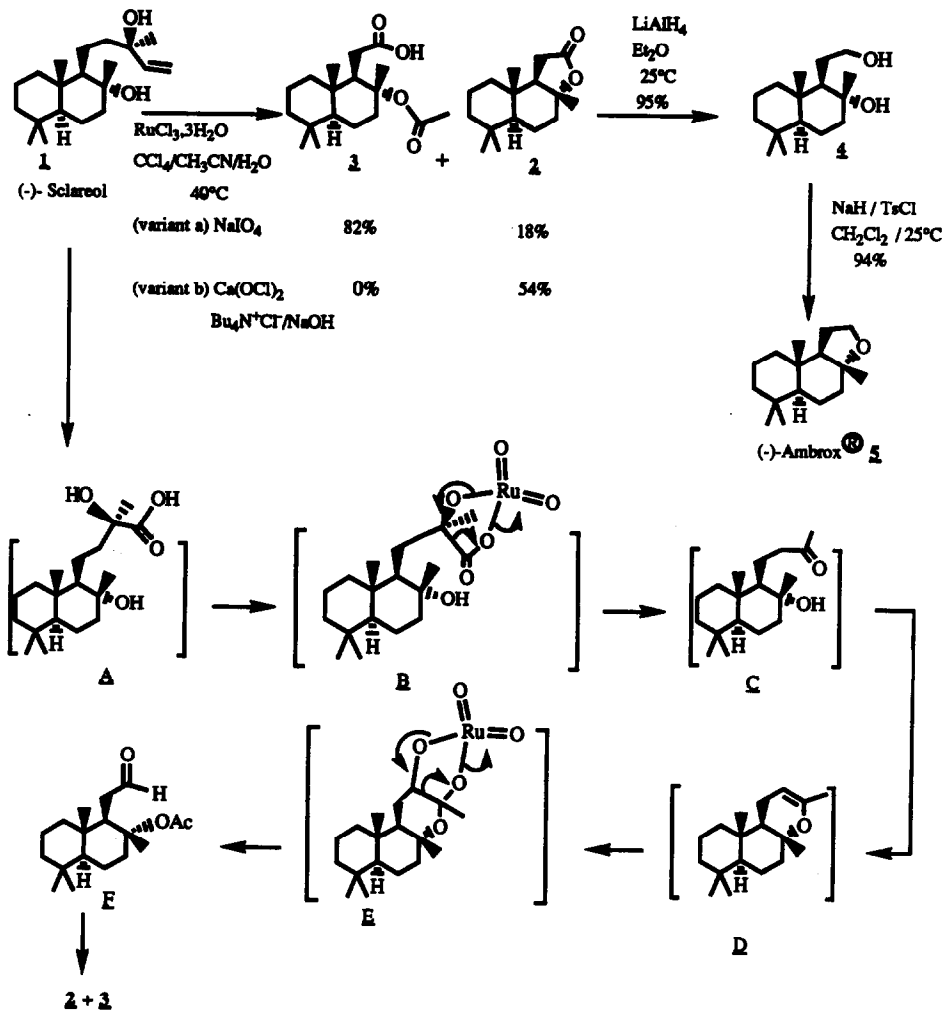
*Nicotiana glutinosa*[16], are usually heading towards (+)-sclareolide **2** or (-)-diol **4** as key intermediates, which then can easily be transformed into (-)-Ambrox®**5**. This first critical step, which involves an oxidative degradation of the side chain of **1**, has so far been effected by using oxidative agents such as ozone[17], peroxides[18], chromium trioxide[19], potassium permanganate[20] or even microorganisms[21]. In addition, two ruthenium oxide catalyzed processes have been reported[22] more recently; it is in this context, that we would now like to report our own results.

We have found that the side chain of (-)-sclareol **1** can be efficiently cleaved with loss of 4 carbon atoms by using the procedure previously described by Silverstein[23] under Sharpless conditions[24] to afford a 82:18 mixture of (-)-acetoxyacid **3** and (+)-sclareolide **2** in 88% yield (variant a).

Since various consecutive slow oxidation steps occur during this reaction, the slow addition of (-)-sclareol **1** to a large excess of in situ generated ruthenium tetroxide is important in order to achieve the indicated yield, which is substantially higher than the one previously reported[22a]. We assume that the degradation of **1** starts with the cleavage of the double bond to give A, which via B leads to the ketol C which under the existing acidic reaction conditions is readily cyclized to D.

Further attack of the double bond in D by ruthenium tetroxide eventually gives rise, via E and F, to the (-)-acetoxyacid **3** as the major product besides a small amount of (+)-sclareolide **2**, the latter resulting most certainly from acid-catalyzed hydrolysis of (-)-**3** and further cyclization. The catalyst, i.e. ruthenium tetroxide, is reduced to ruthenium dioxide during these oxidation reactions and recycled via reoxidation by sodium periodate present in stoechiometric amounts. Accordingly the overall process is catalytic with regard to ruthenium tetroxide.

Since the use of sodium periodate under the above described conditions generates an acidic reaction medium thereby favoring the cyclization of intermediate ketol C to D, it was of interest to test other cheaper reoxidizing agents such as sodium or calcium hypochlorite. It is known,that under such conditions, the active species is either the perruthenate ion $RuO^{-}_{4}$ ($7<pH<12$) or the ruthenate ion $RuO^{2-}_{4}$ ($pH>12$)[25], the latter being unable to cleave a double bond. Furthermore, to avoid the formation of undesired halogenated side-products, caused by the action of hypochlorous acid, it is advantageous to add sodium hydroxide to favor hypochlorite formation. Accordingly, if the reaction was carried out under such basic conditions in the presence of a phase transfer catalyst ($Bu_4N^+Br^-$), (+)-sclareolide **2** was obtained as the sole product in 54% yield, the intermediate (-)-acetoxyacid **3** being readily saponified and cyclized into (+)-**2** (variant b). Both (-)-acetoxyacid **3** and (+)-sclareolide **2** can then be efficiently reduced by lithium aluminium hydride to provide the (-)-diol **4**, which may be cyclized to (-)-Ambrox®**5**. The best results regarding this latter reaction were achieved by using tosyl chloride in methylene chloride in the presence of sodium hydride.




In conclusion, a short and efficient 3-step synthesis of (-)-Ambrox® **5** has been presented[26]. It is based on a ruthenium oxide catalyzed oxidative degradation of the (-)-sclareol side chain affording (-)-acetoxyacid **3** and/or (+)-sclareolide **2** as the key intermediates. The ratio

of 2/3 depends critically on the nature of the reoxidizing agent used and is reversed when going from sodium periodate to sodium or calcium hypochlorite. The overall yields are 79% ($NaIO_4/RuO_4$) and 48% ($Ca(OCl)_2/RuO_4^-$).

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